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EDITORIAL

Issa T, Zalloua P, Issa IA. Resistance reversal: Taiwan's *Helicobacter pylori* trends defy global norms. *World J Gastroenterol* 2025; 31(47): 114789 [DOI: [10.3748/wjg.v31.i47.114789](https://doi.org/10.3748/wjg.v31.i47.114789)]

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MINIREVIEWS

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ORIGINAL ARTICLE**Retrospective Study**

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Randomized Controlled Trial

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LETTER TO THE EDITOR

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Editorial Board Member of *World Journal of Gastroenterology*, Feng Yang, MD, PhD, Associate Professor, Department of Pancreatic Surgery, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai 200040, China. yffudan98@126.com

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Prognostic impact of tumor deposits in colorectal cancer

Bilal Turan

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Bilal Turan, Department of General Surgery, Faculty of Medicine, Suleyman Demirel University, Isparta 32260, Türkiye

Corresponding author: Bilal Turan, MD, Assistant Professor, Researcher, Department of General Surgery, Faculty of Medicine, Suleyman Demirel University, Suleyman Demirel Universitesi Arastirma ve Uygulama Hastanesi, Isparta 32260, Türkiye. bturan117@gmail.com

Abstract

We read with great interest the article by Sun *et al* addressing the prognostic role of tumor deposits (TDs) and negative lymph nodes in N1c colorectal cancer. Their proposal of the NLNTD index is a valuable step toward refining risk stratification in this subgroup. In our recently published population-based cohort of 111106 patients with early-stage colon cancer, TD positivity, classified as N1c according to AJCC definitions, was independently associated with significantly worse overall and disease-specific survival, even after propensity score matching. Taken together, these findings show that TDs are adverse prognostic factors across stages. They should inform treatment planning and follow-up, rather than be regarded as incidental.

Key Words: Colorectal cancer; Tumor deposits; Prognostic factor; Risk stratification; Adjuvant therapy

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Core Tip: Tumor deposits (TDs) are an independent adverse prognostic factor in colorectal cancer across all stages. Evidence from both single-center analyses introducing the NLNTD index and large-scale population-based cohorts consistently shows that TDs should be recognized as high-risk features and incorporated into adjuvant treatment algorithms and follow-up strategies, rather than regarded as incidental findings.

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TO THE EDITOR

Sun *et al*[1] examined the prognostic role of tumor deposits (TDs) and negative lymph nodes (NLNs) in N1c colorectal cancer. The authors focused on the N1c subgroup and introduced the NLNTD index, integrating TDs and NLNs, as a novel tool to refine risk stratification. Although derived from a relatively small, single-center cohort of 107 patients, their study provides meaningful clinical insight into this challenging subgroup.

Our recently published population-based cohort, encompassing 111106 patients with early-stage colon cancer (T1-T3, N0/N1c) from a national registry, demonstrated that the presence of TDs was an independent adverse prognostic factor for overall survival (OS), even after rigorous adjustment through propensity score matching. Furthermore, TD positivity exerted a robust and independent deleterious effect on disease-specific survival (DSS), underscoring its prognostic weight beyond conventional nodal parameters[2].

Emerging data suggest that TDs reflect tumor budding/epithelial-mesenchymal transition, perineural or vascular spread, and stromal-immune remodeling. These processes are closely linked to invasiveness and metastatic potential. Molecular studies implicate TGF- β , Wnt/ β -catenin, and PI3K-AKT dysregulation, together with E-cadherin loss and increased MMP activity. Collectively, these changes indicate enhanced migratory and invasive capacity. The surrounding tumor microenvironment, enriched with cancer-associated fibroblasts and immunosuppressive infiltrates, further facilitates stromal remodeling and dissemination. Consistently, TD positivity tracks with adverse tumor biology and inferior survival, offering a biologic rationale for risk-adapted systemic therapy. Future translational work on molecular markers and signaling nodes may clarify actionable therapeutic targets. These mechanistic insights further justify incorporating TD status and the NLNTD index into postoperative risk stratification and adjuvant therapy planning[3].

While TDs and NLNs are distinct constructs, TDs denoting extranodal tumor foci and NLNs reflecting the extent and quality of nodal sampling, borderline cases, such as TDs adjacent to partially disrupted lymph node capsules, may lead to interobserver variability. Harmonization through multicenter calibration, explicit pathology checklists, and digital pathology quality assurance programs is crucial to ensure consistent classification across institutions. AI-assisted pathology and multiplex immunohistochemistry pipelines may standardize TD/NLN recognition and improve prognostic discrimination.

In clinical pathways, TD positivity and high NLNTD scores could flag candidates for intensified adjuvant chemotherapy and/or closer surveillance schedules. Until prospective validation is available, such use should complement, rather than replace, established guideline factors.

Sun *et al*[1] restricted their analysis to N1c cases and showed that NLNTD predicted disease-free survival, OS, and CSS in this subgroup. Taken together, despite being derived from different patient populations, both studies clearly establish TDs as a powerful prognostic marker.

The broader literature provides similarly compelling evidence[4-8]. A systematic review and meta-analysis by Nagtegaal *et al*[4] demonstrated that the presence of TDs adversely affected survival in stage III-IV colorectal cancer. Belt *et al*[6] and Lino-Silva *et al*[7] further showed that TD positivity in stage II colorectal cancer was associated with markedly worse prognosis, conferring a risk profile comparable to that of stage III disease. More recently, a meta-analysis by Moon *et al*[8] confirmed that TDs constitute an independent adverse prognostic factor for long-term oncologic outcomes.

Effect sizes may differ across stages (*e.g.*, TDs upgrading risk in stage II and refining stratification within stage III) and across demographic strata. Harmonized analyses across regions and age groups are warranted to determine generalizability[2,6,7].

Current guidelines (NCCN/ESMO) define high-risk features to guide adjuvant therapy[9,10]. Accumulating evidence indicates that TD positivity behaves as an adverse prognostic factor across stages, functionally aligning with high-risk biology. While prospective validation is required, recognizing TDs as a high-risk feature could refine adjuvant decisions and surveillance intensity[1,2].

Key limitations include single-center designs and small samples in derivation studies. Multicenter prospective cohorts and, where feasible, randomized trials embedding NLNTD-guided strategies are needed to confirm clinical utility.

Conclusion

Despite different designs and populations, both Sun *et al*'s NLNTD analysis[1] and our large-scale cohort data converge on the same message: TDs are a robust, independent prognostic marker with clear clinical relevance. Explicit recognition of TD positivity as a high-risk feature has the potential to refine adjuvant therapy recommendations, enhance risk stratification, and support more personalized follow-up strategies. Integrating TD and NLN metrics into existing prognostic scores, alongside molecular markers and mutation profiles, could yield more accurate prediction; prospective calibration and clinical net-benefit analyses should precede implementation.

FOOTNOTES

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Country of origin: Türkiye

ORCID number: Bilal Turan 0000-0003-1665-3607.

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